REMARKS

A. Patentability Arguments

I. The Rejections Under 35 U.S.C. § 102(a) Should Be Withdrawn

Claims 89, 102-103, 105-108 and 110-111 are rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Bram *et al.* (WO 98/39361) (Bram *et al.*) for the reasons set forth in the previous Office Action in the rejection of 89, 102 and 107.

The Examiner characterizes Bram *et al.* as disclosing methods of using genetically engineered constructs to regulate B-cell activity through its interaction with cellular receptor ligands and that such constructs can consist of the extracellular domain of the TACI receptor fused to the Fc domain of an immunoglobulin. Bram *et al.* also allegedly discloses that the "subunits" of the construct (*i.e.,* TACI and the Fc domain of the Ig) can be linked by peptide bonds and that it also discloses that the extracellular domain has the amino acid sequence corresponding to about residue 1 to about residue 166 of the consensus sequence of TACI and that the ligand binding region is a sub-fragment of the extracellular domain. The constructs (fusion proteins) are alleged to intercept the normal endogenous ligands that serve to cross-link and activate the TACI proteins on the surface of cells thus inhibiting the ligand's activity. The Examiner concluded that, by utilizing the methods and materials disclosed by Bram *et al.*, one would necessarily inhibit the activity of ztnf4, even though its identity is not known or disclosed in the reference, since ztnf4 is an endogenous ligand of TACI. The Examiner stated that one does not need to know the identity of the TACI ligand in order to practice the method disclosed by Bram *et al.* According to the Examiner, the instant claims only require that the TACI fusion protein be administered to an individual in order to inhibit B cell proliferation and that the composition binds ztnf4. Further, the Examiner stated that Bram *et al.* disclose the administration of the same the compositions for the expressed purpose of inhibiting B cell proliferation (which is a ztnf4 activity). Finally, the Examiner further alleged that since

the fusion proteins disclosed by Bram *et al.* are identical to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention (including the ability to bind the ztnf4 ligand).

Finally, with regard to the limitation "proteins comprising one or more polypeptide fusions" recited in claims 105-106 and 110-111, Bram *et al.* is said to anticipate this limitation since their disclosed fusion protein comprise one polypeptide fusion (*i.e.,* the TACI-Fc fusion protein constitutes a single polypeptide fusion).

The Examiner consequently concludes that Bram *et al.* anticipates all the limitations of the rejected claims.

The Applicants respectfully submit that Bram *et al.* cannot properly anticipate the present invention because it fails to teach certain elements of the claimed invention and because the inherency relied upon by the Examiner is, in the words of the reference itself, only a likelihood.

As regards the present invention, Bram *et al.* presents no data showing how a construct such as those described in the present application can be made, or any data that if made the construct would work to prevent stimulation of B cell activity as is required by the present invention. It does not specifically describe all of the receptors of the present claims. It does not identify ztnf4 or any other ligand. As discussed above, one cannot know from Bram *et al.* key characteristics of the present invention. For example, that disclosure does not provide data showing that the extracellular domain of any ztnf4 receptor will maintain the ability to bind ztnf4 absent the transmembrane and intracellular domains of the receptor and absent proximity with the lipids of the cell membrane. Neither does Bram *et al.* show that the extracellular domain of TACI will function to bind any ligand, let alone ztnf4, either in its full molecule state or when its extracellular portion is fused to an Fc domain of an antibody. Further Bram *et al.* does not teach what particular kinds of Fc fragments may be used in the fusion.

As regards to Bram *et al.*'s alleged inherent anticipation of the present invention, the applicant submits that the reference fails to do so for at least two reasons. First, Bram *et al.* cannot properly, inherently anticipate the claimed subject matter because the Bram et al. does not teach the group of soluble receptors encompassed by the present claims nor does it disclose ztnf4

as a ligand for the receptors. The Bram *et al.* does nothing more than assume that a ligand exists for these receptors and such an assumption is not a proper basis to support a finding of anticipation. Second, as to the role of a ligand for inhibiting lymphocyte proliferation, the Bram *et al.* reference itself states that,

> "The identity of the endogenous ligand of the TACI protein is unknown."

See page 52, line 19.

Further, page 52, line 21, of Bram *et al.* states:

> "This ligand [as yet unidentified] is **likely** to be involved in the regulation of the immune system as well..." *(Emphasis added.)*

Under the law, this admitted likelihood cannot serve as a proper basis for inherent anticipation in that a certain result may occur or become in the prior art is not sufficient to establish inherency of that result or characteristic. See *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 and MPEP § 2112 IV. (The fact that certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.)

The Applicants respectfully submit that both the lack of description of certain elements of the claimed invention and the admitted "likelihood" and its attendant lack of certainty found within the document itself are each legally sufficient to require the withdrawal of the rejections under 35 U.S.C. § 102(a) and withdrawal is respectfully requested.

II. The Rejections Under 35 U.S.C. § 102(e) Should Be Withdrawn

Claims 89, 102-103, 105-108 and 110-111 are rejected under 35 U.S.C. 102(e) as being anticipated by Bram *et al.* (U.S. Patent 5,969,102) (the '102 patent) for the reasons set forth in the previous Office Action in the rejection of 89, 102 and 107.

The Examiner has characterized the '102 patent in that it is similar to Bram *et al.*, the Examiner characterized the inference as described in Section IA above. Therefore, for the purposes of brevity, it will not be repeated here. The Applicants respectfully traverse the rejection for the following reasons.

Inasmuch as the '102 patent is very similar to Bram *et al.* discussed in section IA above, it suffers the same infirmities as Bram *et al.* Like Bram *et al.*, the '102 patent presents no data showing how a construct such as that described in the present application can be made how it would work to prevent stimulation of B cell activity as is required by the present invention. It does not identify ztnf4. It does not specifically describe all of the receptors of the present invention. As discussed above, one cannot know from data presented in the '102 patent the extracellular domain of any of the ztnf4 receptors will maintain their ability to bind its ligand absent the transmembrane and intracellular domains of the receptor and absent proximity with the lipids of the cell membrane. Neither does the '102 patent show that the extracellular domain of TACI will function to bind any ligand, let alone ztnf4 when fused to an Fc domain of an antibody. Neither does the '102 patent teach what particular kinds of Fc fragment may be used in the fusion.

Bram *et al.* cannot properly inherently anticipate the claimed subject matter because the '102 patent does not teach the group of soluble receptors encompassed by the present claims nor does it disclose ztnf4 as a ligand nor any other ligand for the receptors. As discussed above, the '102 patent does nothing more than assume that a ligand exists for these receptors.

As regards the role of a ligand for inhibiting lymphocyte proliferation, the '102 patent itself speaks only in terms of a "likelihood" which is a legally insufficient basis for finding that the reference inherently anticipates the present invention. More particularly, the reference states this.

> "The identity of the endogenous ligand of the TACI protein is unknown."

(Specification, col. 36, lines 55and 56.)

Further, Col. 36, lines 57-59 of the patent states that:

> "This ligand [as yet unidentified] is **likely** to be involved in the regulation of the immune system as well..." *(Emphasis added.)*

As stated above, under the law, this likelihood and its attendant uncertainty cannot serve as a proper basis for inherent anticipation in that a certain result may occur or become in the prior art is not sufficient to establish inherency of that result or characteristic. See *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 and MPEP § 2112 IV. (The fact that certain result or characteristic may occur to be present in the prior art is not sufficient to establish the inherency of that result or characteristic.)

As far as the disclosure of the '102 patent is concerned, the Applicants respectfully submit that while the '102 patent is presumed to be valid under 35 U.S.C. § 282, that such a presumption properly extends only to claimed subject matter and not to every statement set out in the patent specification. The '102 patent does not claim a method of inhibiting B lymphocyte proliferation using a composition comprising a soluble form of a ztnf4 receptor either alone or as a fusion protein and such a disclosure is not entitled to the presumption of validity (*e.g.*, that it meets the statutory criteria for patentability).

Because the '102 patent does not claim the method of the present invention and such unclaimed statements are not entitled to a presumption of validity, and further because the reference only speaks in terms of likelihood of a claimed result the Applicants respectfully submit that it cannot properly anticipate the present invention and thus the rejections under 35 U.S.C. § 102(e) should be withdrawn.

III. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

The Examiner has maintained the rejection of claims 89 and 102-111 under 35 U.S.C. 103(a) as being unpatentable over Bram *et al.* (W0 98/39361) (Bram *et al.*), as cited above, in view of Presta *et al.* (U.S. Patent 5,739,277, (the '277 patent)) as well as the combination of the '102 patent and Presta.

The Examiner described Bram *et al.* and the '102 patent as set out above.

The Examiner also stated that Bram *et al.* differs from the claimed invention in that they do not disclose the specific use of IgG1 heavy chains or TACI extracellular sub-fragments consisting of amino acid residues 25-104 or 1-154 in fusion proteins. However, as discussed above, Bram *et al.* and the '102 patent disclose merely a "likelihood" that a ligand they might find would likely be involved in regulation of the immune system.

The Examiner characterized the '277 patent as disclosing methods of making fusion proteins comprising the Fc portion of an immunoglobulin (including IgG1). The '277 patent further discloses that the Fc portions of the various immunoglobulins have an increased circulatory half-life. Presta *et al.* teach that the Fc portions of the various immunoglobulins can be used interchangeably.

The Examiner concludes that it would have been obvious for one of skill in the art at the time of the invention to modify the teachings of Bram *et al.* or the '102 patent to include the teachings of Presta *et al.* because it is within the skill of the art to modify B cell activity (*i.e.*, reduce B cell proliferation) by administering TACI receptor fusions comprising the Fc portion of an immunoglobulin, and because Presta *et al.* teach it is within the skill in the art to construct and use fusion proteins comprising the Fc portion of IgG1. Further, the Examiner alleges that one would have been motivated to do so in order to achieve the expected result of generating TACI/Fc fusions functional in the methods disclosed by Bram *et al.* that have the increased circulatory half-life as disclosed by Presta *et al.* and that there would have been a reasonable expectation of success in combining the disclosure of Bram *et al.* with that of Presta *et al.* to obtain TACI/IgG1 Fc fusion proteins that are functional in the methods taught by Bram *et al.* and the '102 patent.

The Applicants respectfully traverse the rejection and request reconsideration because as discussed above Bram *et al.* and the '102 patent are fatally defective as an anticipatory references for the methods of the present invention.

The Applicants reiterate that both Bram *et al.* and the '102 patent fail to disclose key elements of the present invention and thus are not proper references under either 35 U.S.C. § 102(a) or 102(e), respectively. Because they are not proper references under § 102(a) or (e), they cannot provide a proper basis for any rejections under 35 U.S.C. § 103 even when combined with Presta, because Presta fails to remedy all of the infirmities of either allegedly anticipating reference. Presta does teach the use of Fc fragment as fusion with other protein to increase the circulating half-life of other molecules it does not provide the requisite information regarding *inter alia,* whether ztnf4 exists, whether a soluble form of a ztnf4 receptor can bind its ligand absent any other protein domain of the receptor. It also does not disclose whether or not any

subfragment of any receptor at all would work as is required for the practice of the present invention. As discussed in Section II above, the cited references do not discuss whether or not the extracellular domain of TACI (or any other ztnf4 receptor) or any subfragment of that domain, when missing one or more other protein domains and/or absent any interactivity with cell surface lipids would or could function to bind any ligands.

On that basis, the Applicants submit that the references fail on numerous counts to provide a proper basis for rendering the present invention obvious and therefore that all of the rejections under 35 U.S.C. § 103 are improper and should be withdrawn.

IV. The Rejections Under 35 USC § 112, First Paragraph, Should be Withdrawn

Claims 89 and 102-111 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain(s) subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated that the claims are drawn to a vast genus of soluble forms of ztnf4 receptors. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that the Applicants have possession of the claimed invention. The Examiner stated that to adequately describe the genus of soluble forms of ztnf4 receptors, Applicants must adequately describe not only what constitutes a soluble ztnf4 receptor but also what constitutes the ztnf4 ligand. However, the Examiner alleges that the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of soluble ztnf4 receptors to which the claims are drawn, such as a correlation between the structure of the receptors and its recited function (*i.e.,* inhibiting B-cell proliferation and binding ztnf4), so that the skilled artisan could immediately envision, or recognize at least a substantial number of

members of the claimed genus. The Examiner states further that the claims are drawn to the use of any soluble protein comprising a sequence substantially identical to the ztnf4 receptor in a method for inhibiting B lymphocyte proliferation and that the specification discloses that three polypeptides, BR43x2, TACI and BCMA are disclosed to be able to bind ztnf4. However, the Examiner asserts that the specification is silent as to which, if any, of these three receptors can inhibit B cell proliferation. The Examiner also alleges that the specification does not place any structure, chemical or functional limitations on the variants of ztnf4 receptors nor does the recitation of "ztnf4 receptor" convey a common structure or function. Further, the Examiner stated that the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted (*e.g.,* TACI and BCMA). Moreover, the Examiner alleges that the specification and the claims fail to provide any guidance on the structure of the polypeptide and what changes can or cannot be made and retain the recited function further stating that structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure and the claims and that no common structural attributes identify the members of the genus. Since according to the Examiner the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the function of the binding of ztnf4 alone is insufficient to describe the genus of "soluble ztnf4 receptor" polypeptides that function equivalently. One of skill in the art would reasonably conclude that the disclosure of three sequences: SEQ ID NO:6 (TACI), SEQ ID NO:8 (BCMA) and SEQ ID NO:4 (BR43x2), fails to provide a representative number of species of soluble ztnf4 receptors to describe the claimed genus.

The Examiner concluded that because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicants were in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by the Applicants in the specification; nor has the Applicants shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicants described distinguishing

identifying characteristics sufficient to show that Applicants were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of more than one species within the genus. Therefore, the Examiner concluded that because the art is unpredictable, in accordance with the *Guidelines*, the description of soluble forms of ztnf4 receptors is not deemed representative of the genus of polypeptides to which the claims refer.

The Applicants respectfully traverse the rejection and request reconsideration in view of the fact that the claimed soluble receptors have in fact been characterized as to their amino acid sequences and by certain common features, they share the ability to bind ztnf4 working examples have been provided, and the specification provides sufficient written description of changes that can be made in the receptors to support the claims to a genus of soluble receptors.

As regards the alleged "vast genus" of soluble forms of ztnf4, the Applicants are puzzled as to how the Examiner concluded that such a genus would be vast. The Applicants have identified and sequenced three receptors that bind ztnf4, BCRx4, TACI and BCMA have identified the transmembrane domain and the intracellular domain of the receptors and characterized structural features of receptors as well as shared features including ligand binding characteristics. (See Figure 1)

For example, Figure 1 shows common structural features of the disclosed receptors, including the number and location cysteine repeats common to certain of the receptors, the location of the transmembrane domains, the extracellular ligand binding domain of the receptors which are the soluble form of the receptors (cite). Example 10 of the specification shows that the soluble forms of that BCMA and TACI receptors bind ztnf4.

Further, the specification explicitly sets out illustrative examples of modifications that can be made to the receptors. For example, page 27 of the specification describes in detail a variety of "substituted homologues" of BR43x2 polypeptides having,

> "...50%, preferably 60%, more preferably 80%, sequence identity to the sequences shown in SEQ ID NOS:2 and 4 on their orthologs. Such polypeptides will more preferably be at least 90% identical at and more preferably 95% or more identical to SEQ ID NO:2 or its orthologs."

The specification also teaches how identities are calculated, and page 20 of the specification describes the kinds of substitutions, deletions and additions that are preferred stating that

> These changes are preferably of a minor nature, that is conservative amino acid substitutes. (See Table 4)

The Examiner also states that the specification is silent as to which, if any, of these three receptors inhibit B cell proliferation. However, the Applicants submit that any of the claimed receptors, which bind zntf4 will inhibit B cell proliferation because they bind circulating ztnf4 and thus make it unavailable to bind to B cell surface receptors which is necessary to stimulate B cell proliferation.

Because the specification explicitly describes a variety of ztnf4 receptors and how they can be made and used, and because the specification describes receptors that are representative of the genus and further because the binding of ztnf4 to a soluble receptor makes it unavailable to induce B cell proliferation, the Applicants respectfully submit that the claims fulfill the requirements of 35 U.S.C. § 112, first paragraph, and, therefore, submit that the rejections thereunder should be withdrawn.

Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance and early notification is requested.

Respectfully Submitted,

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